INSTITUTE OF PUBLIC HEALTH

COLLEGE OF MEDICINE AND HEALTH SCIENCES

UNIVERSITY OF GONDAR

TITLE: ASSESSMENT OF FACTORS ASSOCIATED WITH MORTALITY AMONG VISCERAL LEISHMANIASIS AND MALARIA CO-INFECTED PATIENTS IN NORTHWEST ETHIOPIA; A RETROSPECTIVE STUDY

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A THESIS SUBMITTED TO THE SCHOOL OF PUBLIC HEALTH, COLLEGE OF MEDICINE AND HEALHT SCIENCES, INSTITUTE OF PUBLIC HEALTH, UNIVERSITY OF GONDAR IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTTER OF PUBLIC HEALTH.

JUNE, 2017

NORTHWEST ETHIOPIA

Acknowledgments

I would like to express my deepest gratitude to my advisors Mr. Mekuriaw Alemayehu

(Msc, PhD candidate) and Mr. Kindie Bantie (BSC, MSc) for their guidance on this thesis development and also Gondar University for giving me this chance. I also thanks Medecins Sans Frontieres- Holland, giving the chance to collect data and abdurafi project staffs for giving guidance and checking the availability of data for this study. Special thanks for Mr. Teferi Molla; data encoder at abdurafi MSF-H kala-azar, HIV/AIDS and Malnutrition Project. I also have many thanks to Koert Ritmeijer, Lindsay and Uday Mukerhj

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Abbreviations

DAT	Direct Agglutination Test
L-AMB	Liposomal Amphotericin B
MSF	Medecins Sans Frontieres
MSF-H	Medecins Sans Frontieres Holland
MSF-OCA	Medecins Sans Frontieres- Operation Center Amsterdam
RDT	Rapid Diagnostic Test
VL	Visceral Leishmaniasis
WHO	World Health Organization
SSG	Sodium Stibo Gluconate
SP	Sulphadoxin Pyramethamine
Ig E	Immuno Globulin E
HMS	Hyper reactive Malarial Splenomegaly
HIV	Human Immuno Deficiency Virus
HIV/AIDS	Human Immuno Deficiency Virus/Acquired Immune Deficiency Syndrome
BSC	Bachelor of Science
SPSS	Statistical Packages for Social Science

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Abstract

Introduction: Visceral leishmaniasis (VL) and malaria co-infection is common in VL endemic areas. The occurrence of this two parasitic disease simultaneously occurred on the same host at a time resulted in sever clinical presentation and poor or delayed prognosis and finally may lead to death. It is reported that there is co-infection of these two disease in all endemic regions of the world.

Objective: The objective of this study was to identify factors associated with mortality among visceral leishmaniasis and malaria co-infected patients from 2010-2016 in northwest Ethiopia.

Methods: A retrospective study was carried out. Data were extracted from routinely collected patient's records by Medicines Sans Frontiers Holland between 2010 and 2016 in northwest Ethiopia. A total of 123 VL-malaria co-infected and 387 VL-Mono infected randomly selected patient's record were reviewed. Data were entered into EPI INFO 7, analyzed using SPSS. Both bivariable and multivariable logistic regression analysis was done. A p-value less than 0.05 was taken as statistical significant with 95% confidence level.

Results: A total of 510 VL patients' medical records reviewed, 123 VL-malaria co-infected and 387 VL mono infected patients were studied. Among them 25 deaths recorded (10 from exposed group 15 from none exposed group), with case fatality rate of 8.1% and 3.8% respectively. Malnutrition (AOR=69.11: 95%CI: 3.39, 1406) and splenomegaly (AOR: 0.16, 95%CI 0.04, 0.86) were associated with the mortality.

Conclusions and Recommendation: Malnutrition and splenomegaly was associated with the VL-malaria coinfection associated deaths. Health professionals should be good enough when doing physical examination, balanced and adequate nutrition for co-infected patients is very mandatory.

Keywords: Co-infection, VL-malaria, retrospective, Northwest Ethiopia.

1. Introduction

1.1. Problem Statement

The geographic overlap in the occurrence of leishmaniasis and malaria was reported in endemic areas.[1, 2] Leishmaniasis and malaria cases are prevalent in South Asia, Latin America [3-5]. Visceral Leishmaniasis (VL) together with malaria is common in east African countries with prevalence of 20%in Uganda, 26.2% in Sudan.[6, 7].6% in India and <1% in Bangladesh [8].

The co-infection is presented with from the potential diagnostic delay to significant clinical implications and increased level of disease-related morbidity and mortality [7]. Co-infected patients presented at hospital with deteriorated clinical pictures and side effects of the drugs also challenging as compared to mono-parasitic infections[9].

World Health Organization (WHO) estimates that from about 900,000 to 1.3 million new leishmaniasis cases, 200,000 to 400,000 visceral leishmaniasis and 700,000 to 1.2 million cutaneous leishmaniasis case loads annually in the world. Among the cases 90% were found in six countries; India, Bangladesh, South Sudan, Sudan, Brazil, and Ethiopia [10]. The disease burden is very high in east Africa which accounts 29,400 to 56, 600 cases annually. Sudan shares nearly half of east African leishmaniasis cases estimated 15,000-20,000 yearly [11]. Visceral leishmaniasis is one of the re-emerging public health problem in Ethiopia after index case known the first time in 1942 in the southern Ethiopia [12]. Currently estimated 3700-7400 new leishmaniasis cases and 3.2 million people at risk annually. The northwestern lowland of Ethiopia have more than 60% cases clustered. In this region poor, seasonal young migrant workers are more affected [13, 14].Malaria is the leading prevalent and killer parasitic disease, caused by four main plasmodium species namely *Plasmodium falciparum, Plasmodium vivax, plasmodium malarae,* and *plasmodium ovale.* Globally half billion people at risk with 289 million at high risk in 2015 and 212 million cases per year and 429 000 deaths. Among all deaths 90% occur in WHO African region [15].

However the basic information lacks in Ethiopia about the co-occurrence and outcomes of malaria and Visceral leishmaniasis. This study were identified factors associated with mortality among VL-malaria co-infected patients. The study area is highly endemic for malaria and more than 60% of the country's VL burden.

1.2. Literature Review

Malaria is commonly occurred in VL patients in endemic areas [3]. There is some evidences of VL-malaria co-infection all over the world. VL-Malaria Co-infection is higher in Africa. 26% in Sudan and nearly 20% in Uganda. From VL-Malaria co-diagnosed patients in Sudan 3.5 % of whom died, while lower fatality rate among controls, 2.8% [6, 7]. No difference in case fatality among cases and controls, 3.5% & 2.8% and 2.7% & 3.1% in Sudan and Uganda respectively.

Study done in Sudan showed that co-infected patients treated with arthemeter and quinine to treat malaria were 13 to 15 fold mortality risk than treated with artesunate + sulfadoxine-pyrimethamine (SP). Of those died patient's higher density of leishmaniasis parasite in their lymph nodes and bone marrow was found to be increasing the mortality risk [7]. There also seen elevated serum Immuno Globulin E (IgE) response in malaria patients irrespective of helminth infection and its correlation with high malaria parasite load and helminth egg density. Malaria infection is also a strong driver of IgE production as compared to helminthes [16]. In Malawi children diagnosed with cerebral malaria and HIV coinfection more (23%) case fatality rate than 17% none HIV infection children. Cerebral malaria is a major contributor to malaria deaths [17]. *Plasmodium yoelii* Malaria and cutaneous Leishmaniasis (*Leishmaniasis .amazonesis species*) co-infection among trial mice in Brazil was found to be 30% death from cases, while 100% survival among the control groups [3].

Visceral leishmaniasis, and malaria are well known health problems in the lowlands of Ethiopia, currently these diseases spreading to the adjacent semi-lowland and highland areas. The 2005-2007 outbreaks of VL in south Gondar zone, Adiszemen area is the typical example, which leads hundreds for death [18].

VL is most sever forms of leishmaniasis which affects the reticuloendothelial systems, in low socioeconomic portion of the population, In Bangladesh, about 33.3% (4/12) confirmed deaths didn't get leishmaniasis treatment[19].

Globally over 40 million people displaced in 2015 as a result of natural disaster, war and violence related to religious and ethnic conflicts. Internal displacement in sub Saharan Africa leads people to potential health problems, like malaria and leishmaniasis

[20].Studies showed that cross border movement is highly associated with malaria infection [21]. Clinical malaria also observed in people with history of travel to malaria endemic areas [22]. Migration of daily laborers to and from endemic areas, HIV, Malnutrition, climate and environment change affects VL disease distribution and progression rate[23].

Major agriculture projects and mechanized farms, ongoing mega projects have main benefits in economic advancement, but the control and prevention measures of infectious tropical diseases is poor[24].

Abdurafi is a place which many young migrant workers travel every year for sesame and cotton harvesting. Evidences in northwest Ethiopia showed that the highest prevalence of VL cases was from Autumn (September to November) followed by Winter (December to February) with lower prevalence in spring (march to May) [13]. Similar study showed that November to May was peak seasons for the VL-Malaria co-infection because malaria occurs during or immediately after rainy season and VL more common in dry season. So health professional need alertness in diagnosing both diseases in endemic areas, presenting with prolonged fever, hepatosplenomegaly and lymphadenopathy all over the year including the ability to diagnose the atypical presentation of leishmaniasis to prevent delay[24].

Leishmaniasis- malaria co-infection resulted in leishmaniasis driven effects may change the immune response regulated by these disease, as a result there also be delayed prognosis[25]. Emaciation, jaundice & anemia [7]. Anorexia, malaise, vomiting, more severe symptoms and young age males was most significantly affected group which have association for co-infection [6, 26]. Study suggest that patients aged between 12 and 18 months, with platelet counts below 85,000/mm3, and respiratory abnormalities at admission should be considered potentially severe [27].

There was multiple positive correlation in pro-inflammatory vs. type-1 cytokines and pro-inflammatory and type 2- cytokines exhibited in Sudanese patients.[28] Risk of death is high in VL patients associated with weakness, old age ($\geq$ 60), bleeding, and jaundice [29]. Previous exposure to plasmodium infection was found to be a predictor for the manifestation of malnutrition in under-five children [30]. Visceral leishmaniasis is misdiagnosed or mimics with many febrile illnesses like, chronic malaria, hyper reactive

malarial syndrome (HMS), shistosomiasis, typhoid fever miliary tuberculosis and brucellosis[13].

Occurrence of the co-infection alters the natural outcome and progression of diseases due to modulation of immune response [5]. In patients co-infected by HIV, malaria and leishmaniasis faced significant complications on the treatment of those diseases, in that protozoan parasites enhance the fast replication of the HIV leading to AIDS stage and on the other hand HIV changes the pathogenesis of malaria and leishmaniasis causing parasites[23, 31]. In the same way VL is the commonest opportunistic infection in HIV patients in VL endemic areas. Eastern Africa has the largest VL-HIV caseload in the world **[**32].

The overall case-fatality rate in patients treated by AmBisome was 6.6% increased by half (3.3%) from non HIV infected patients related with poor treatment outcome were HIV infection, bleeding and a previous VL episode [33]. Similarly patients with visceral leishmaniasis and HIV coinfection who treated by SSG exhibited 43.9% cure rate. 31.6% and 14% parasitological treatment failure and case fatality rate respectively.[34]Death, treatment failure was found to be high specially in severely ill (unable to walk) and HIV-VL co-infected patients in northwest Ethiopia[35]. pancreatitis is the common side effect of SSG [36]**.** Sodium stibogluconate (SSG) was found to be 75% effective in Northwest Ethiopia for longer duration. VL recurrence mostly occurred in Metema, West Armachiho and Humera areas which is common VL and malaria focus, bordering Sudan and Eritrea.[37].

Visceral leishmaniasis patients co-diagnosed with hepatitis B or C have significantly increased levels of AST, ALT. also decreased level of platelet and albumin level[38]. Sever malaria is a major cause of mortality in children [39].HIV and malaria infected hospitalized children in Tanzania exhibited delayed malaria parasite clearance[40].Atypical presentation of VL is high when there is co-occurred with other infections and there is under diagnosis of VL, leading patients to leishmaniasis associated morbidity and mortality [41]**.**

Leishmaniasis is the second parasitic killer next to malaria and the fifth opportunistic disease in the world [37]. Visceral leishmaniasis is a neglected disease caused by protozoan parasites. It occurs worldwide including Africa, Asia, Europe and Latin

America[2]. If there is no early diagnosis and treatment leishmaniasis is highly fatal disease. But with proper treatment it is curable [13]. VL treatment drug side effects negatively affects the quality of life of patients living with HIV/AIDS in Northern Ethiopia [42].

However, VL-Malaria co-infection researches are limited all over the VL and malaria endemic focus areas including Ethiopia. There is scarcity of information and there were expected mortality of these co-infection. So this study were assessed the factors associated with mortality among VL-Malaria co-infected patients in northwest Ethiopia.

Conceptual Framework

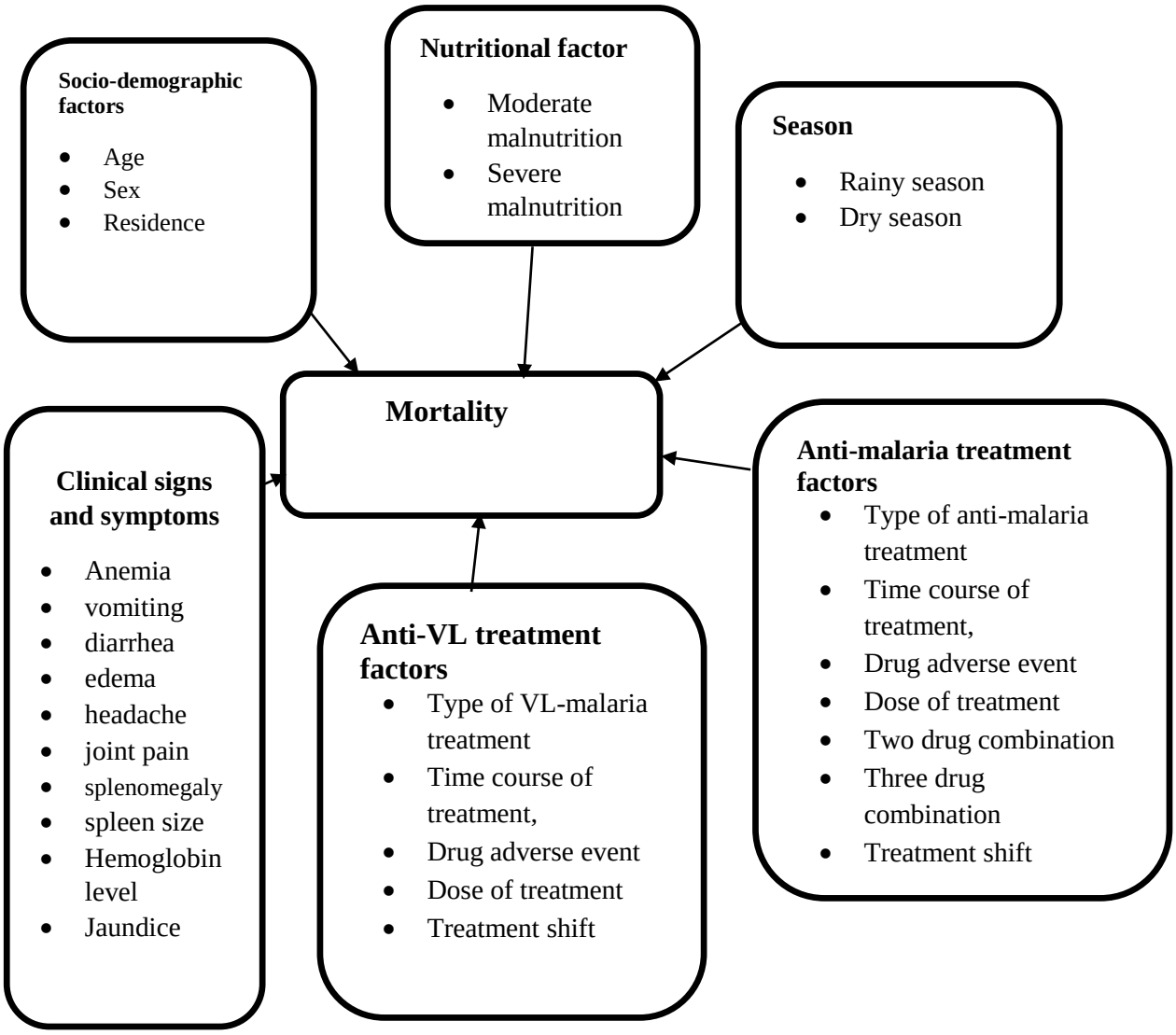

Figure 1: Conceptual framework factors associated with mortality among VL-malaria co-infected patients. Developed after different literatures reviewed [3-7]

1.3. Justification

Visceral leishmaniasis and malaria is commonly occurred in VL endemic areas. As studies showed that there is occurrence of the coinfection in the study area. Despite the fact that some studies done to address this area of concern. But the factors associated with mortality is not investigated in endemic areas of Ethiopia.

If there is misdiagnosis and delay Leishmaniasis is more than 95% fatal disease if untreated early. Malaria also have significantly fatal, in 2015 there was 429,000 deaths from malaria globally, and WHO African region shares 92% of it, and most deaths were due to Falciparum malaria which is very common in the study area. If it is co-occurred at a time the severity and response to treatment may be very challenging.

Studies conducted previously were not much enough to describe about factors associated with mortality among co-infected patients and it was done in different population, in Sudan, Uganda, and Malaysia.

This study was investigated the factors associated with mortality among VL-Malaria co-infection in northwest Ethiopia. The finding may also serve as an important tool for any possible interventions aimed at improving good clinical and treatment outcomes of co-infected patients.

2. Objective

Assessment of factors associated with mortality among Visceral Leishmaniasis patients co-infected with malaria who were admitted in MSF-Holland Abdurafi kala-azar, HIV/AIDS and malnutrition project from 2010 to 2016, Northwest Ethiopia.

3. Methods and Materials

3.1. Study design

Retrospective cohort study was carried out from patient records. Visceral leishmaniasis and malaria co-infected and VL mono-infected patients were included in this study. Patients with laboratory confirmed diagnosis of both VL and Malaria at hospital admission or during hospital stay was taken as exposed, whereas, laboratory confirmed VL and having laboratory confirmed negative malaria laboratory test result were none exposed.

3.2. Study area and period

The study area is located in northwest, Ethiopia with Latitude 13°43'60.0"N (13.7333300°) and Longitude 36°27'00.0"E (36.4500000°) in Amhara region, Mirab Armachiho district, bordered south by Metema, west by Sudan, north by the western Tigray, northeast by Tegede district, and on the east by Tach Armachiho. Abdurafi is one of the town in west Armachiho district found north, 27km, 250km and 995km far from Abrhajira (center of the district), Gonder and Addis Abeba respectively. Abdurafi has one Government health center, one nongovernmental humanitarian medical organization (MSF-Holland) kala-azar, and malnutrition and HIV treatment center (Hospital) about 15 private clinics.

Every year as many as 300,000-500,000 daily laborers migrate for commercial cotton and sesame farms, the harvesting season in the farming area of Abdurafi, near the Sudanese and Eritrean border. Their work and living conditions are extremely basic and leave them vulnerable to fatal diseases like VL.

Medecins Sans Frontiers-Holland is giving voluntary medical, humanitarian service by giving free treatment for VL, Malnutrition, HIV/AIDS and other emergencies in collaboration with Ministry of Health since 1997 in northwest Ethiopia. Outreach services on VL and malnutrition control & prevention and many randomized controlled trials in collaboration with (Drugs for Neglected Disease Initiative (DNDi) are the projects main tasks in the area. This hospital has 100 beds and five wards for admission and treatment of Leishmaniasis, leishmaniasis-HIV co-infection, Leishmaniasis- complicated malaria, Tuberculosis and complicated sever acute malnutrition patients.

3.3. Source Population

The source population of this study was patients who were admitted in MSF-H kala-azar, HIV/AIDS and Malnutrition project for diagnosis and treatment from January 1, 2010 to December 31, 2016G.C.Total patients admitted and treated from 2010-2016 were10458, 2383 of them were leishmaniasis patients.

3.4. Study Population

Subjects were all laboratory confirmed visceral leishmaniasis and/or malaria patients. Who were admitted in abdurafi MSF-H VL, HIV/AIDS and Malnutrition project between January 1, 2010 and December 31, 2016.

3.5. Inclusion Criteria

All VL patients who were confirmed by laboratory investigations (rK39 and/or DAT for primary visceral leishmaniasis b

ut Bone marrow, spleen aspiration or lymph node aspiration for relapse and/or if failed serologic test but fulfilling the WHO VL case definition. Incomplete data that was expected to be meaningful for analysis included in the study, but still if there is difficulty to give meaning the data were excluded because of incompleteness.

3.6. Exclusion Criteria

Patients those who have more than 40% incomplete data in the diagnosis, treatment and socio demographic characteristics were excluded from this study. Patients those who have third morbidity HIV and TB was excluded from the study to avoid confounding effect on the outcome variable.

3.7. Sample Size and Sampling Procedure

The sample size was determined by using from previous similar study done in Sudan and that were give the highest sample size. % of outcome in unexposed group= 20%, outcome in exposed group: 33.3%, Odds ratio=2, Confidence level=95%, Power= 80% and Ratio unexposed to exposed 3:1 then using EPI-Info version 7 population survey unmatched cohort formula, given that 480, with the addition of 5% attrition rate it was 504. Finally data was collected from 510 study subjects (123 exposed and 387 none exposed groups). Simple random sampling method was used. Samples were selected using Openepi, random number generator.

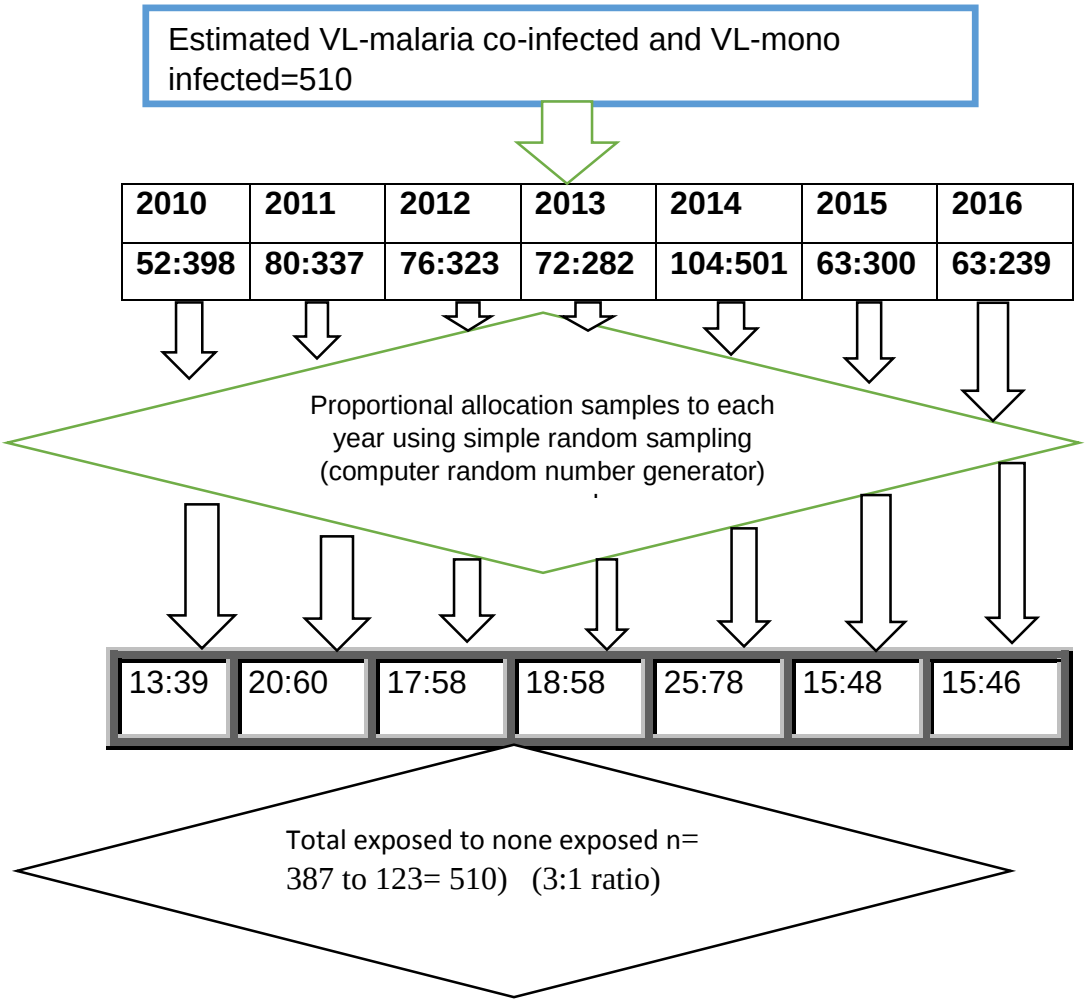

Figure 2. Schematic presentation of sampling procedure.

3.8. Study variables

3.8.1. Outcome variable

Mortality

3.8.2. Explanatory variables

A. Socio-demographic variables

Age, sex, residence

B. Clinical signs and symptoms

Anorexia, Anemia, malaise, vomiting, diarrhea, parasite load, spleen size, cough, CBC profile, Pancreatitis, Jaundice, Poor appetite

C. Malaria and VL treatment related factors

Type of anti-malaria treatment, time course of treatment, drug adverse event, dose of treatment, Two drug combination, three drug combination, treatment shift

D. Nutritional factor

Severe malnutrition

Moderate Malnutrition

E. Season related factors

Dry season, Rainy season

3.9. Data collection

Data was collected on the routine patient care registry by MSF-Abdurafi Kala-azar, HIV/AIDS and Malnutrition project. After selecting the sample data was taken from the patient charts as well as Medecines Sans Frontiers Operational Center Amsterdam databases (MSF-OCA) by using readymade data extraction sheet after ethical clearance from MSF-OCA and University of Gondar institution review board obtained. Patients diagnosed by RDT and/or microscopically positive malaria test and serologically and/or parasitological tested positive. VL-mono infected group was selected randomly from VL-none malaria patients diagnosed and treated in the study period. Sociodemographic details, clinical signs and symptoms, nutritional status, treatment season, laboratory test results, medical treatments and its outcomes was extracted.

3.10. Data Quality Assurance

Two BSC nurses for data collection and one health officer for supervision was recruited for data extraction. Training about data extraction procedure was briefly communicated. The supervisor and the data extractors were checked and clean the data after end of each data extraction date.

3.11. Data processing and analysis

After data collection extraction sheets were collected from data collectors, coded and cleaned for its completeness. Then data entered to EPI info version 7 and imported to SPSS version 20 statistical software packages by principal investigator.Counts, tables were used for the descriptive summary. Binary logistics regression model were fitted. A p-value of <0.05% was used to say significantly associated between the explanatory and outcome variables with 95% confidence level.

An association between the dependent and independent variables was assessed by both binary and multiple logistic regressions and strength of its association was presented using odds ratio with 95% confidence level. Factors statistically significant at 0.2 in the bivariable logistic regression model remained in multivariate model to control the effect of confounders.

3.12. Operational Definition

Exposed; Positive parasitological demonstrated parasites in a lymph node, spleen, or bone marrow aspirates or Positive direct DAT (Direct Agglutination Test) and/or positive rk39-based rapid test for VL and RDT and/or microscopically confirmed malaria parasite from blood smear.

None-exposed: Visceral leishmaniasis mono infected group were laboratory (serologically or parasitological) confirmed VL but malaria RDT or thick or thin smear microscopic confirmed negative test result.

Anemia; Anemia is defined as the hemoglobin level less than the reference level (<10g/dl) in tropical settings. None - mild (Hgb ≥7.3 g/dl), Moderate (Hgb 5.3-7.2 g/dl), Severe (Hgb<5.3 g/dl). (WHO)

Rainy season: The rainy season in Ethiopia covers from June to September.

Dry season: October to May is dry season relatively in Ethiopia climate condition

Co-infection: Coinfection may result when hosts are independently infected by different parasites at the same time or when interactions among parasites species facilitate co-occurrence.

Cured; A definitive cure is the absence of visceral Leishmaniasis signs and symptoms and a negative test of cure 6 months after initial cure, and absence of malaria sign and symptoms.(definitive cure). Free of sign and symptom after end of VL treatment and Malaria confirmed by laboratory test or clinical confirmation by Doctor or Health officer.

Death/Mortality: patient dead due to or its complications of either by malaria and/or VL which was confirmed by Doctor or Health Officer during hospitalization period and having death certificate.

Resident: One who reside in a particular place permanently or for an extended period for equal to more than two years.

Migrant worker: A person who moves to area in order to find employment in a particular seasonal or temporarily. (Less than two years in the area source: MSF-H working criteria).

Splenomegaly: spleen enlarged below left costal margin considered to be have splenomegaly, most commonly the spleen is palpable by the second week of illness and, depending on the duration of illness, it becomes hugely enlarged([43]

4. Ethical Considerations

Initially ethical approval and permission letter was obtained from Research Ethical Committee of University of Gondar and from Medecins Sans Frontiers-Holland (MSF-H) Ethical Review Board then formal letter got from University of Gondar (UoG) and email confirmation from MSF-H before the study. The study participant's data were reviewed by trained health professionals kept confidentially, personal identifiers was masked and were not used for any other purpose other than this study.

5. Results

5.1. Socio demographic characteristics

A total of 510(123 VL-malaria co-infected (exposed) and 387 VL-None malaria (None-exposed) patients were studied. A total of 2383 patient's diagnosed and treated for VL hospitalized in Medicines Sans Frontiers Holland abdurafi Kala-azar, HIV and malnutrition project, northwest Ethiopia from January, 2010 to December, 2016.

Total of twenty five deaths registered (10 from VL-malaria co-infected and 15 from non-malaria VL co-infected) with case fatality rate of the coinfection was 8.1% versus 3.8% among unexposed group.

Among the total patients 98.4 %(n= 121) were males from exposed and 98.4(n=381) from non-exposed).The mean age of 24.1 years (SD±7.9) for VL-malaria co-infected patients and 25.3(±7.8) for VL mono infected patients. More than half of the patients (54%) were within the age of 20-29 years. Amhara region residents were 87.3%through period of their illness before admission and more time live in the area, followed by (n=28, 5.5%) from Tigray region and the rest (n=2, 0.2%) were came from Sudan.

Among 510 included study participants 418 (78.4%) were diagnosed by serologic tests for VL were made by rK39 (DiaMed IT-Leish) (n=418, 78.4 %), DAT on (n=42, 8.2%) and Microscopic direct parasite observation (n=70 13.7%). From total aspirations spleen aspirates (n=52, 10%), Bone marrow aspirates (n=18, 3.5%). Malaria was confirmed by (n=274, 53.8%) by rapid diagnostic tests (RDT) microscopically with thin and thick blood film (n=236, 46.2%). Among exposed group 68% (n=85) species was *P.falciparum* resulted in cause to death of (n=6, 60%), followed by (n=2, 20%) *P.vivax* and (n=2, 20%) with *P.falciparum* and *P.vivax* mixed infections during admission or through time of hospitalization. Most patients (n=72, 58.5% and n=220, 56.8%) were hospitalized from June to September.

Most (n=481, 94%) diagnosed as primary VL 23 of them died, 2 deaths recorded from relapses. From the total VL confirmed patients (n=123, 24.1%) were co-infected with malaria.

Table 1. Socio demographic and other variables frequency with its percentage, among abdurafi-MSF-Holland Kala-azar, HIV/AIDS and Malnutrition project (2010-2016), northwest Ethiopia.

Variables	Categories	VL-malaria co-infected		Non-Malaria VL	
		Frequency	%	Frequency	%
Age in years	0-9	5/122	4.1	9/384	2.3
	10-19	23/122	18.7	66/384	17.1
	20-29	65/122	52.8	210/384	54.3
	>=30	29/122	23.6	99	25.6
Gender	Male	2/122	1.6	381/387	98.4
	Female	121/122	98.4	6/387	1.6
Season on admission	Dry season	72/122	58.5	220/387	56.8
	Wet Season	50/122	43.2	167/387	43.2
Malnutrition	BMI<18.5(MAM + SAM)	36/123	29.3	195/385	50.4
	BMI $\geq$ 18.5	87/123	70.7	190/385	49.4
Splenomegaly	Yes	105/120	85.4	302/386	78
	No	15/120	12.2	84/346	21.7
Anemia level(admission) (Sever, Moderate,, mild or No anemia)	(Hemoglobin <11g/dl	107/123	87	344/383	88.9
	Hemoglobin >=11g/dl	16/123	13	39/383	11.1
Residence status	Migrant worker	62/120	50.4	140/386	36.2
	Resident	58/120	47.2	246/386	63.6
Admission spleen size(BCM)	0-3cm	32/123	26	127/386	32.8
	4-5 cm	34/123	27.6	105/386	27.1
	6+	57/123	46.3	154/386	39.8
VL type	Primary VL	110/121	89.4	371/386	96.1
	Relapse VL	11/121	8.9	15/386	3.9

Table 2. VL-Malaria and VL none malaria patients showed clinical symptoms and death status, in abdurafi MSF-Kala-azar, HIV and malnutrition Hospital, Ethiopia (2010-2016).

Clinical signs and symptoms		VL-Malaria		None Malaria-VL		Total
		Dead	Not dead	Dead	Not dead	
Vomiting	Yes	0	1	0	0	1
	No	0	112	15	372	499
Headache	Yes	1	2	0	0	3
	No	9	111	15	372	498
Diarrhea	Yes	1	0	0	0	1
	No	9	113	15	375	489
Splenomegaly	Yes	6	11	3	81	100
	No	4	99	12	290	405
Joint pain	Yes	0	3	0	1	4
	No	10	110	15	367	492
Edema	Yes	0	3	0	8	11
	No	10	110	0	364	484
Sever Weakness	Yes	3	34	2	46	85
	No	7	78	13	324	422

Majority 111 (90.2%) of the patients who live in Amhara region during time of admission were co-infected with VL and malaria, majority were in west Armachiho district (n=110, 89.4%). Anemia (hemoglobin level <10.9 g/dl) was a very common condition in both groups (87% and 89.7%), exposed and non-exposed respectively. Average duration of hospital stay relatively high among VL-malaria co-infected group (33.9, SD=±22.4) as compared to VL mono-infected group (Mean=30.2 days, SD= ±14.6).

Bivariable and Multivariable logistic regression analysis

Significant associations were found between death and variables Splenomegaly and malnutrition during admission (BMI<18.5) among the co-infected group by bivariate and multivariate logistic regression analysis. Other variable which show significant association with the outcome variable by bivariate analysis were hemoglobin level <11g/dl, Season on admission and residence status (being migrant worker). See table 3

Malnutrition is the main risk factor which leads VL-malaria co-infected patients 69 times more likely to die than VL-mono infected patients (AOR. 69.11, 95% CI 3.39, 1406).

Patients those who had enlarged spleen below the left costal margin at the left upper quadrant (AOR=0.1: 95% CI 0.01, 0.86) were 90 times less likely to die in reference with no palpable spleen among the VL-malaria co-infected patients. But unlikely for patients with VL only. (AOR= 1.01, 95% CI 0.26 to 3.82).

Most deaths recorded in wet season among co-infected group (8, 80%) but season on admission was not risk factor for mortality, (AOR=3.63, 95%CI: 0.49, 26.60). which means the co-infection had no difference with VL-mono-infected group (AOR= 1.14, 95% CI 0.39-3.37) and (n=8, 53.3%)as compared to dry season. with the case-fatality rate of being co-infected was 8.1%. Most Co-infected and none co-infected groups in the wet season (n=32, 64% and n=82, 49.7%) respectively was sever to moderate malnutrition with body mass index (BMI) of <18.5. No statistically significant difference on death among Sever, Moderate and mild malnutrition's (BMI<16 <17 and <18.5 respectively). *P.falciparum* Malaria was the leading cause of death from malaria species among co-infected group.

Table 3. Bivariable and Multivariable analysis of VL-malaria co-infected and VL-mono infected patients at Abdurafi MSF-Holland kala-azar, malnutrition and HIV/AIDS project, Ethiopia (2010-2016), Northwest, Ethiopia.

Variables	Exposed				Non-Exposed			
	Not dead	Dead	COR (95% CI)	AOR (95% CI)	Not dead	Dead	COR (95% CI) Crud	AOR (95% CI) Adjusted
Residence								
Resident	52	6	1	1	233	13	1	1
Migrant Worker	59	3	0.44(0.10, 1.85)	0.73(0.11, 4.92)	138	2	0.26(0.05,1.16)	0.28(0.06, 1.29)
Season								
Dry season	70	2	1	1	212	8	1	1
Wet season	42	8	6.66(1.35,32.88)	3.63(0.49,26.60)	160	7	1.15(0.41,3.26)	1.14(0.39,3.26)
BMI								
BMI≥18.5	27	1	1	1	191	4	1	1
BMI <18.5	86	9	28.6(3.47,236.6)	69.11(3.39,1406)*	179	11	2.93(0.91,9.38)	2.85(0.87,9.27)
Hgb level								
>=11g/dl (No anemia)	13	3	1		35	4	1	
<11 g/dl (mild to severe anemia)	100	7	0.30(0.07,1.32)	0.07(0.005, 1.02)	333	11	0.28(0.08,0.95)	0.34(0.10,1.18)
Splenomegaly								
No	11	4	1	1	81	3	1	1
Yes	99	6	0.16(0.04, 0.68)	0.10(0.01,0.86)*	290	12	1.11(0.30,4.05)	1.01(0.26,0.86)

1= reference, *: Showed the significant variable with p-value of less than 0.05, 95% CI

6. Discussion

In this study the main findings were malnutrition BMI<18.5kg/m^2 and absence of splenomegaly were risk factors for death. The co-infection from the co-infected group. Leishmania mostly affects low socioeconomic countries and where it often co-exists with chronic malnutrition.

On the other hand malaria and leishmaniasis are the two most important public health problems in the world. Chronic malnutrition is one of the main risk factors for developing the disease. Leishmania is fatal protozoan disease if left untreated cause morbidity and mortality as a result of malnutrition by exposing the host to impairments of the disease defense mechanism [44].

Few studies have been published on VL-malaria coinfection, on the relationship between leishmaniasis progression and malnutrition and malaria coinfection. Most patients exhibited poor prognosis after admission with the presence of malnutrition it may worsen to a condition with sever diseases stage and death as evidenced by average length of hospitalization days of VL-Malaria co-infected patients were higher than the none-exposed group. This is similar finding with a study done on VL in northern Ethiopia. [45]

P.falciparum were the major protozoan malaria causative agent among the total VL malaria co-infected patients. Previous studies had similar findings with this fact that was done on children past exposure of the *plasmodium* had significant impact on nutritional status of children [46].

In this study malnutrition had risk factor for death of 24% exposed group than none exposed group (AOR=69.11, 95% CI: 3.39-1406 and AOR=2.85 95 % CI 0.87, 9.27 respectively).VL was found to be decreased level of the serum nutrients as a comparative study showed in Bangladesh on serum iron. In fact both parasites use red blood cells for their survival mechanism. Progressively leads to low iron deficiency anemia with low oxygen carrier hemoglobin as evidenced by this study most (87%) exposed and 89% non-exposed group were anemic [47]. Body mass index measures the body's fat accumulation as this study patients were severely wasted, Evidences showed that protein malnutrition is the most deleterious cause of malnutrition in developing countries. Also considered to be the first risk factor for the development of clinical visceral leishmaniasis (VL) and

favorable environment for the replication of the L.donovani species, Malnutrition (BMI<18.5) was identified as a risk factor for concomitant VL and malaria co-infection related deaths.

Those patients who had palpable spleen below the costal margin were negatively correlated with the co-infection and death. This is in agreement with Erika van den Bogaart et al. from those who investigated the VL-malaria coinfection in the same study populations. Those who have no splenomegaly were more suffered from the co-infection this may be because of early arrival to health institutions may be due to the increased intensity of disease progression to seek health care earlier. This is in line with Erika van den Bogaart et.al on the similar study in Sudan and Uganda done among surveys on hospitalized patients [6, 7]. On the other hand there may be negligence or under care of patients by health care workers with no splenomegaly, since splenomegaly is one of the clinical case definition of VL.

The in-hospital case-fatality rate was significantly higher (8.1% among exposed and 3.1 none exposed). The case fatality rate among the co-infected group in this study was higher than the Sudanese and Ugandan patients (8.1% vs. 2.7%, 3.5% respectively). The difference may be resulted in the people are quite different genetically, in this study almost half were migrant workers originated from highland areas and low immune for malaria and Leishmania infections, while the Sudanese patients were reported as residents in the area that may make them to develop partial immunity for this two parasitic diseases. As a result the disease progression may be slower and low risk to death. May be the sample size and the method used may bring the difference in case fatality in this two studies. But the case fatality of this study was lower case fatality rate than co-infection trial mice in Brazil, 30% death from cases, while 100% survival among the control groups.[3]

Limitations of the study

This study was used secondary data so that some important variables missed because of the incompleteness from patient records like some clinical variables jaundice, edema.

7. Conclusion

Malnutrition is the most common risk factor for VL-malaria co-infections associated deaths. More than 90% of VL-malaria patients had malnutrition with BMI of <18.5kg/m2. Patients who had non palpable spleen size were higher probability of death among VL-malaria co-infected than VL-mono infected patients.

Recommendations

There should be VL and malaria preventive measures, treatment of visceral leishmaniasis in Government health institution in endemic areas. Balanced and adequate nutrition for those who have VL and malaria co-infected patients should be very mandatory in household level as well in health institutions who have patient admission wards.

Health professionals in endemic areas should get appropriate training by the woreda health office/zonal health department and Medecins Sans Frontieres Holland project during VL-malaria patient examination and diagnosis. Immediate treatment of malaria and VL co-infected patients who have none palpable spleen should be in place.

I. Zonal health department; should schedule training sessions in endemic areas for health professionals

II. Woreda health office should arrange health care workers training, follow up, supportive supervision and provision of logistics.

III. MSF-Holland should actively participate in the training process by budget allocation, arranging trainer, practical training on patients.

IV. Health professional's needs to be work as the updated of Ethiopian government VL and malaria guidelines, read and update the governments sustainable development goals to achieve as planned.

V. Regional health Bureau and Federal Ministry of Health: should find solutions for the availability of VL drugs in all government hospitals.

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9. ANNEXES

Annex 1: Information sheet

Research description: This is a study focusing on **visceral leishmaniasis and malaria co-infection associated mortality in Northwest Ethiopia.**

Name of Principal Investigator: Melkamu Amare

Sponsor: Self

Name of Organization: University of Gondar

Purpose of the study: To assess co-infection of malaria and visceral leishmaniasis mortality associated factors. To suggest possible strategies to improve co-infected patients treatment improved treatment.

Procedure: Institution based retrospective study was conducted after getting Ethical clearance from University of Gondar and permission from Medecins Sans Frontieres- Holland ethical review board.

Risks: There were no foreseeable risks to the health institutions and on patients since the study only involves review of medical records.

Benefits: There had no special benefits to the health institutions. However, the management of the health institutions will get the final report and be able to identify which areas they need to improve according to research information.

Confidentiality: Confidentiality of information is guaranteed in that the information collected were accessible to the principal investigator and trained data collectors.

Compensation: No compensation was available for any process of data collection but we are very grateful to the health institutions for taking part in this study.

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Annex 2: Assurance of the investigator

I, the undersigned, MPH student declare that this thesis is my original work, except where otherwise acknowledged, this thesis has not been submitted for another degree award in this or any other university or institution.

Name: _____

Signature: _____

Date: _____

Place of submission: Institute of public health, College of medicine and Health Sciences, University of Gondar.

Date of submission: _____

This thesis work has been submitted for examination with our approval as university advisors.

Advisors:

Name	Signature
1. Mr. Mekuriaw Alemayehu (MSC, PhD candidate)	_____
2. Mr. Kindie Bantie (BSC, MSC)	_____

Annex 3. Data extraction sheet

Assessment of factors associated with mortality among VL-malaria co-infected patients data extraction sheet at abdurafi MSF Holland Kala-azar, HIV/AIDS and malnutrition project (2010-2016).

	Data extraction sheet, 2017	***Code***	***Remark***
	Variables		
	Socio Demographic cxs		
1	Sex		
	Male		
	Female		
2	Age in years		
3	For how long lived in current place in years		
	Residency status		
	Resident		
	Settler		
	Migrant worker		
4	Region of origin for migrant workers		
	Amhara		
	Tigray		
	Oromiya		
5	Benshangul		
	SNNP		
	Other		
	SIGNS AND SYMPTOMS		
	Duration of symptoms before admission in months		
	SIGNS AND SYMPTOMS after admission		
	Malaise		
	Yes		
3	No		
	Vomiting		
	Yes		
	No		
	Diarrhea		
	Yes		
4	No		
	Headache		
	Yes		
5	No		
	Edema		

	Yes		
6	No		
	Joint pain		
	Yes		
7	No		
	Skin rash		
	Yes		
8	No		
	Fever		
	Anemia Yes/no		
	Splenomegaly		
	Yes		
	No		
	if yes Spleen size (BCM) in cm		
	Hepatomegaly		
	Yes		
	No		
	Diagnostic laboratory tests for VL		
	RK39		
	positive		
	Negative		
	DAT test		
13	Negative		
	Borderline		
	Infection intensity in lymph node aspirate		
14	Infection intensity in Bone marrow aspirates		
15	Infection intensity in spleen aspirates		
16	Diagnostic laboratory tests for Malaria		
	Blood film		
	Negative		
	PF		
	PV		
	PF + PV		
	Rapid diagnostic test(RDT)		
	Negative		
	PF		
17	PV		
	PF + PV		
	CBC profile at admission		
	WBC(number		
	RBC(Number)		
18	Platelate(number)		

	Hemoglobin(number)		
	hematocrit(number)		
	CBC profile during discharge		
	WBC		
19	RBC		
	Platelet		
	Hemoglobin		
	hematocrit		
	Season of treatment		
	Autumn		
20	Spring		
	Summer		
	winter		
	Body mass index (BMI) at admission		
	Body mass index (BMI) during discharge		
	Degree of malnutrition		
	None		
	Mild		
	Moderate		
	Severe		
	Weight		
	weight in kg during admission		
	weight in kg during discharge		
	previous Medical treatment for VL		
	Yes		
	No		
	If yes When		
	year of treatment		
24	Treatment outcome		
	Cured		
	Default		
	Referred		
	Relapse		
	Type of Anti-leishmaniasis drugs		
	AmBisom only		
	Duration:		
	AmBisom + Meltifosin		
	Duration:		
	SSG only		
	Duration		
	SSG + Paramomycin		

	previous medical treatment outcome		
	cured		
	default		
	Referred		
	relapse		
	Previous anti-malarial treatment		
	Yes		
	No		
27	If yes When?		
	year of treatment		
	Type of anti malaria treatment		
	Artesunate + SP		
	Artemether		
28	Quinine		
	Artesunate		
	Artemether + lumefantrine		
	Treatment outcome		
	cured		
29	default		
	Transferred to other stracture		
	relapse		
	Type of Current treatment		
	Type of Anti-leishmaniasis drugs		
	AmBisom only		
30	Duration:		
	AmBisom + Meltifosin		
	Duration:		
	SSG only		
	Duration		
	SSG + Paramomycin		
	Current anti malarial treatment		
	Artemether		
	Quinine		
	Artesunate		
	Artemether + lumefantrine		
	Severity scoring		
33	prognosis		
	Very poor		
	poor		
	good		
	Very good		
	Final treatment outcome for current treatment		

	cured		
	Default		
34	Relapse		
	Transferred to other stracture		
	Dead		
	Concomitant diagnosis		
	Acute respiratory infection		
35	Yes		
	No		
	Ear,Nose and throat infection		
	Yes		
	No		
	Skin infections		
	Yes		
	No		
	Tuberculosis		
	Yes		
	No		
	If yes on treatment or treated		
	Yes		
	No		
	If yes type of IP		
	Amoeba		
	Giardia		
	Strongloids		
	hookworm		
	Shistosomiasis		
	Yes		
	No		
	HIV/AIDS		
	Yes		
	No		
	If yes on ART		
	Yes		
	No		